Remarks/Arguments

The present amendment amends claims 1, 3, 5, 21-26, and 28-34. The amendments are intended to address the comments provided by the examiner.

Claims 1, 5, 21-23, 26, 28-30, 33 and 34 were amended to replace consists or consisting "of an amino acid sequence of SEQ ID NO: 1" with --of SEQ ID NO: 1-- .

Claim 3 was amended to be independent and directly incorporate the description of the polypeptide immunogen providing protective immunity. Claim 3 previously depended from claim 1, where claim 1 indicated the polypeptide immunogen provided protective immunity.

Claims 3 and 31 were amended to indicate "the amino".

Claims 23 and 30 were amended to remove reference to "up to".

Claim 24 was amended to be dependent on claim 3 and to directly indicate the polypeptide is substantially purified. Claim 24 previously provided the polypeptide being substantially purified based on its dependency on claim 19, and directly included the same polypeptide immunogen description provided in claim 3.

Claim 25 was made dependent on claim 24, and claim 32 was made dependent on claim 31.

Claim 31 was amended to be independent and directly incorporate the descriptions of the polypeptide providing protective immunity and being substantially purified. Such descriptions were previously provided in claim 31 based on claims 26 and 27.

Claim 33 was amended to replace "by with up" to --by up--.

35 U.S.C. § 112, First Paragraph (Written Description)

Claims 1-3, 5, 7, 19-23, and 26-30 stand rejected as allegedly lacking written description. The patent office argues that polypeptides having any degree of structural similarity are "not necessarily expected" to have similar properties absent a concrete structure-function correlation, that applicants have failed to advance any arguments to address the art-recognized unpredictability documented in the multiple references, and one cannot speculate that polypeptide having a high degree of structural similarity are expected to have similar properties. The rejection is respectfully traversed.

The ability of SEQ ID NO: 1 to provide protective immunity illustrates that SEQ ID NO: 1 is a representative antigen commensurate with the scope of the claims. The provided rejection fails to present any arguments as why one skilled in the art would expect a significant number of polypeptides within the scope of claimed genus not to provide protection. Instead, the rejection is improperly based on the possibility that a well placed alteration may potentially impact the ability of the claimed polypeptide to provide a protective immune response.

For example, the patent office is taking the position that in theory SEQ ID NO: 1 may contain a critical amino acid out of the 260 amino acids, where alteration of the amino acid results in SEQ ID NO: 1 no longer providing protective. Assuming for the purposes of the argument there is a single critical residue, the odds of such a residue being altered is 1/260 or about 0.3%. In such an instance, the 99.7% of the polypeptides within the genus of one amino acid alteration retains the ability to provide protection.

Furthermore, SEQ ID NO: 1 is 260 amino acids in length and may contain more than one epitope providing a beneficial effect. Epitopes providing beneficial effects could include one or more B-cell epitopes and one or more T-cell epitopes. The T-cell epitopes would drive a cell mediated response involving the presentation of short antigens on antigen presenting cells.

The importance of similar structures having similar activities is acknowledged by the patent office in its 102(e) rejection. The 102(e) rejection is based on a polypeptide having an overlap of 3 amino acids with SEQ ID NO: 1. The patent office argues the ability to provide protective immunity is an inherent property inseparable from the structural identical prior art sequence. The pending claims provide for far more than a three amino acid overlap.

US2006-0177462

The patent office cites to US2006-0177462 as documenting the functional unpredictability associated with variants of staphylococcal polypeptides. According to the patent office, the reference indicates that a particular polypeptide having about a 90% identity to a protective polypeptide is not protective. To the extent that US2006-0177462 indicates that a particular polypeptide having about a 90% identity fails to provide protection, applicants note that the present claims do not cover 90% identity.

US2006-0177462 also includes data supporting the ability of polypeptides having similar structures to provide protective immunity. The data illustrates the ability of polypeptides based on the COL ORF0657n sequence to protect against different heterologous isolates of *S. aureus,* such as Strain Becker and clinical isolates. (See for example, US2006-0177462, Example 3, Figures 3A-3B and description of the figures provided in paragraph [0034]; Example 6, Figures 4A-4H, and description of the figures provided in paragraph [0035], and Table 3 at columns 28 and 29.) Strain Becker ORF0657n has a sequence identity of 95% to the COL ORF0657n sequence. (US2006-0177462, Table 3, at column 12.) The different clinical isolate *S. aureus* strains have an ORF0657n differing from COL ORF0657n by up to 94%. (See the description of Figures 4A-4H provided in paragraph [035], and Table 3 on columns 28 and 29.)

The ability of a polypeptide to induce an immune response against a heterologous strain demonstrates that different closely related sequences are expected to provide protection. The corresponding challenge strain ORF0657 sequence would be expected to also induce an immune response, for example, when used in a homologous challenge. The expectation is based on a homologous challenge involving the use of a polypeptide immunogen having the same sequence as the challenge strain, where in a heterologous challenge the sequence used to induce the immune response is different from that actually present.

Applicants note that US2006-0117462 is a copending patent application currently undergoing patent prosecution with the same examiner as the present case. Applicants have no objection to the patent office referencing data provided in US2006-0177462.

Applicants object to the patent office in the present case presenting arguments regarding predictability of the scope of alterations to the SEQ ID NO: 1 polypeptide provided in US2006-0177462. On page 12, of the present rejection, the examiner argues that:

> Thus, the unmodified SEQ ID NO: 1 when merely split into a fragment of amino acids 82-486, or amino acids 42-196, looses its protective capacity, **indicating the critically of retaining all the amino acid residues of SEQ ID NO: 1 intact within the claimed fragment/variant** in order to retain the requisite function of providing protective immunity against *S. aureus*. **Thus, there is a lack of predictability as to whether polypeptide variants having up to 10% non-identity to SEQ ID NO: 1 anywhere along SEQ ID NO: 1** would remain immunospecific to *S. aureus* and provide protective immunity against *S. aureus* in a human or a non-human host. [Emphasis added.]

Such arguments are specially directed to the scope of alterations to SEQ ID NO: 1 provided in US2006-0177462, and are not a recitation of facts provided in US2006-0177462. Applicants disagree with the examiner's position, based on the heterologous protected data mentioned above and other arguments presented in the US2006-0177462 file.

Additional References

The patent office relies on Skolnick *et al.* (*Trends in Biotechnology* 18:34-39, 2000), Colman P.M. (*Research Immunol.* 145:33-36, 1994), and Houghten *et al.* (New Approaches to Immunization, *Vaccines 86,* Cold Spring Harbor Laboratory, pages 21-25, 1986), in arguing for unpredictability. The cited references are silent as to the likelihood that a significant number of longer-length polypeptides, shown to be protective, would be rendered no longer protective if a small number of alterations are introduced. The possibility that some unknown alteration to an amino acid residue may impact a particular protein-antibody interaction, does not equate to a significant number of polypeptides within the scope of the claims losing the ability to provide protective immunity.

Coleman P.M. is argued by the patent office to indicate unpredictability in protein antibody interactions, where the alteration occurs in the active site or outside the active site (e.g., affects folding). Coleman P.M. does not address the question as whether a significant number of polypeptides would lose the ability to provide protection if some identified alterations were made.

Houghten *et al.* was cited for teaching the importance of individual amino acid residues and their position in peptide-antibody interactions. Absent from Houghten *et al.* is any indication as to the likelihood a limited number of alterations would generally be expected to render a polypeptide no longer protective.

In the office action dated August 5, 2009, the examiner indicates Houghten on page 24 asserts.

> One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is

> precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool.

(Office Action dated August 5, 2009, at page 8.) The asserted language is two sentences pieced together (shown in bold below). The overall language in the context used by Houghten *et al.,* appears to highlight the potential effect of multiple mutations and is directed to the system employed:

> If the range of decreased binding ability after single point mutation of a protein antigen varies in a manner similar to that found in this model system, **one could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance to the binding interaction of the altered residue**. It can be suggested that "antigenic drift" is the result of mutations at a relatively small number of amino acids, but more importantly, relatively noncritical amino acids, in the antigenic determinant. In "antigenic shift," the large number of amino acid changes in the primary sequence may not be as important as the fact that the large number of changes eventually lead to a "break" in antigen recognition through the loss of an essential antigenic residue and consequent loss of existing immunological protection. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in a loss of protection. The loss of binding ability with two point replacement analogs in our model system results in a decrease in binding, which is approximately the two relative decreases multiplied together. **A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool**. Detailed examinations of other antibody-antigen systems are being carried out to establish the existence of general trends in peptide antigen recognition patterns. [Emphasis added.]

Skolnick *et al.* was cited as indicating the difficulty in assigning functional activities for a particular protein based on sequence homology even where there is a similar overall structure. Skolnick *et al.* concerns assigning a function to a protein based on the presence of a sequence characteristic of a certain function and the molecule's overall structure. Skolnick *et al.* does not discuss protein antibody interactions, and does not provide any indication as to whether a skilled artisan would predict whether an alteration to a protective polypeptide would render the polypeptide no longer protective.

35 U.S.C. § 112, First Paragraph (New Matter): Claim 5 and dependent claims

Claim 5 stands rejected as allegedly containing subject matter not described in the specification is such a way to reasonably convey to the skilled artisan the inventor at the time the invention was filed possessed the claimed invention. The rejection is directed to reference in the claim to "wherein said sai-1 region is present on a sequence found in a *S. aureus* sequence". The office action alleges the claim refers to a region different from a sai-1 polypeptide region having at least one of three specifically recited properties, for which the application allegedly fails to provide descriptive support. The rejection is respectfully traversed.

Claim 5 was previously amended to more particularly describe the additional region or moiety as being different from a "sai-1 polypeptide region", by defining the excluded sai-1 polypeptide region as present on a *S. aureus* polypeptide sequence having at least 30 contiguous amino acids as provided in SEQ ID NO: 1. Support for the amendment is provided in specification as follows:

> Reference to "additional region or moiety" indicates a region or moiety different from a sai-1 region. The additional region or moiety can be, for example, an additional polypeptide region or a non-peptide region.

(The specification at page 3, second paragraph.)

> Different sai-1 sequences may be present in different strains of *S.* aureus. Two examples of sai-1 sequences are provided by SEQ ID NO: 7 and 8. Other naturally occurring sai-1 sequences can be identified based on the presence of a high degree of sequence similarity or contiguous amino acids compared to a known sai-1 sequence. Contiguous amino acids provide characteristic tags. In different embodiments, a naturally occurring sai-1 sequence is a sequence found in a *Staphylococcus*, preferably *S. aureus,* having at least 20, at least 30, or at least 50 contiguous amino acids as in SEQ ID NO: 1; and/or having at least 85% sequence similarity or identity with SEQ ID NO: 1.

(The specification at page 6, fourth paragraph.)

Support for the additional region or moiety that is present having a property recited in the claims is provided, for example, in present application on page 3, first paragraph. The excluded sai-1 polypeptide region is different from the additional region or moiety having a property recited in the claim.

35 U.S.C. § 102 (Granoff et al.)

Claims 1, 5, 7, 19, 21-23, 26-30, 33 and 34 stand rejected as allegedly anticipated by Granoff et al. (US 7,534,444) ('444). The rejection is based on interpreting reference to consisting of "an amino acid sequence of SEQ ID NO: 1" to encompass a fragment of any length of SEQ ID NO: 1. Granoff et al. ('444) is cited for providing a sequence consisting of QTP which is a fragment of SEQ ID NO: 1. The rejection is respectfully traversed.

The claims were amended to more clearly include a reference to the polypeptide of SEQ ID NO: 1.

35 U.S.C. § 112, Second Paragraph

Claims 3, 4, 24, 31, 33 and 34 stand rejected as allegedly indefinite.

a) Claim 33 is indicated to be incorrect based on reference to "by with". Claim 33 was amended to remove reference to "with".

b) In claims 3, 24, and 31, the examiner suggested replacing "amino terminus" with --the amino terminus--. Claims 3 and 31 were amended as suggested by the examiner. Claim 24 was made dependent on claim 3.

c) & d) Claims 3, 24 and 31 were argued by the examiner to improperly provide for more alterations than base claim 1. Claims 3 and 31 were made independent. Claim 24 was amended to depend from claim 3.

e) Claims 4 and 34 were rejected based on the alleged indefiniteness to claims 3 and 33. Claims 3 and 33 were amended as noted above.

Please charge deposit account 13-2755 for fees due in connection with this amendment. If any time extensions are needed for the timely filing of the present amendment, applicants petition for such extensions and authorize the charging of deposit account 13-2755 for the appropriate fees.

Respectfully submitted,

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